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This observational study involves the evaluation of a cohort of patients who had undergone a modified radical mastectomy for primary breast cancer and then underwent a contralateral subcutaneous mastectomy at the time of reconstruction. The study extends clinical follow-up to a minimum of 10 years, methodically reviews the histology of the primary mastectomy and contralateral mastectomy materials and compares the cohort to several control groups treated "conventionally" without contralateral subcutaneous mastectomy. Initial evaluation of the cohort demonstrates a remarkable disease free survival compared to similar patients with similar tumors not exposed to contralateral subcutaneous mastectomy. The survival advantage is observed to be maximal the closer the second procedure was performed to the primary mastectomy, mitigating against the result being due to time to procedure selection bias. The study of the contralateral specimens for frequency and pattern of epithelial hyperplasia associated with contralateral cancer and the cataloguing of findings is being carried out to establish a resource for in-situ molecular studies on such unique material associated with whole gland evaluation.

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FOREWORD

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Kenneth Scott McCall 8/12/97

PI - Signature Date

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INTRODUCTION

This project is designed to study a unique cohort of patients who underwent modified radical mastectomy of a cancerous breast and contralateral subcutaneous mastectomy followed by reconstruction of both breasts with silicone-silastic implants. Several studies have looked at contralateral mastectomy as a therapeutic option driven principally on the basis of the risk of a contralateral second breast cancer (1,2,3). The frequency of synchronous second cancers is insufficient to warrant the procedure. Survival differences would be (1). The present study is designed to consider the effect of the bias associated with the period elapsed from the time of the first mastectomy to the time of the removal of the second breast. The present study is also concerned with evaluation of the histopathological features of the primary mastectomy and the histopathology of the contralateral specimen in relationship to observed clinical outcome.

The ongoing controversy regarding silicone breast implants is a factor which was considered in evaluating the cohort in the present study (4,5). The initial evaluation of the patients and the follow-up information accrued was intended to examine whether there was an adverse effect on patient survival, disease free survival or quality of life with contralateral subcutaneous mastectomy and silicone implants. The issue was initially whether women with breast implants developed connective tissue disorders (6,7,8), but some suggested early in the controversy that there may be increased risk of cancer associated with silicone implants (9). The accumulating evidence is that there is no increased risk of cancer, and that there may even be a reduced risk (10,11). This later concept has been questioned, but remains an interesting issue (12), stimulated further by the preliminary analyses of the present study group. Two large epidemiologic studies have suggested that the connective tissue scare associated with silicone implantation was based on questionable assumptions (13,14). The controversy continues. In any event the present proposal involves women who have had silicone/silastic implants.

The data to date suggests that survival advantage is accrued with less lead time to second mastectomy rather than longer periods as would be predicted if the effect was due to lead time bias. The preliminary data analyses mandate that the cohort be studied rigorously to determine if the apparent survival differences are confirmed and if they extend into the longer period of follow-up. Irrespective of survival differences, the specimens associated with this cohort may provide insight into breast tissues contralateral to a diagnosed breast cancer.

In order to evaluate the potential significance of the preliminary data, the present study compares the bilateral mastectomy cohort with additional control groups with similar tumors and patient characteristics, but treated with 1) unilateral mastectomy, 2) segmental mastectomy, or 3) segmental mastectomy with radiation. The control group utilized in the preliminary evaluation consisted of matched patients treated with unilateral modified radical mastectomy.

The present project is specifically intended to extend the follow-up of the cohort of patients who had undergone unilateral modified radical mastectomy followed by contralateral subcutaneous mastectomy and reconstruction with silastic/silicone implants to a minimum follow-up of ten years and to compare these to the control groups identified. An important component of this project is the cataloguing of the pathologic specimens and the characterization of the frequency and pattern of epithelial hyperplasias and atypias in the contralateral breast.

METHODS

Contralateral Subcutaneous Mastectomy Population

The study group consists of 360 consecutive patients who underwent contralateral subcutaneous mastectomy between 1975 and 1986 at Duke University Medical Center performed by Dr. Nicholas Georgiade, Dr. Ronald Riefkohl or Dr. Gregory Georgiade. Of these patients, 67 demonstrated only in situ carcinoma. The mean age of the patients at operation was 42.9 years old. The primary breast cancers were treated by modified radical mastectomy. The second breast (contralateral) mastectomy was followed by bilateral reconstruction with silicone gel filled, silastic implants.

Control Groups

The initial control group used in the preliminary analyses were derived from a cohort of patients who underwent unilateral modified radical mastectomy for regional breast cancer at Duke University. These were consecutive patents drawn from the surgical schedule lists. Additional control groups are to be assembled from patients from the NSABP statistical center from protocol B-04 and B-06 to include matched controls for age, tumor type and stage treated with mastectomy (C2), tylectomy (C3), or tylectomy with radiation (C4). Patients are excluded from the control groups (C1-C4) if they experienced metastatic disease within 3 months of diagnosis, or had previous or simultaneous breast cancer; subsequent contralateral breast cancer (diagnosed > 3 months following primary breast cancer).

Follow-Up Procedures

Follow-up contact is by telephone interview combined with medical record review, abstraction, and verification of deaths by death certificates.

Definitions

The variables are defined as follows:

1) Disease-free interval (DF-SURV) = Time in years from unilateral cancer surgery to either recurrence of disease or date of last follow-up, whichever comes first.

2) Survival (SURV) = Time in years from unilateral cancer surgery to last follow-up or death

3) Age at operation (AGEOP) = Age of patient in years at the time of unilateral cancer surgery.

4) Nodal status (NODES) = Number of involved lymph nodes observed at the time of unilateral cancer surgery.

5) Tamoxifen status (TMOX) = Whether or not the patient was treated with tamoxifen as part of cancer therapy.

6) Adjuvant therapy (ADJV) = Whether or not the patient received adjuvant therapy, type recorded; dicohotomized use or no use.

7) Operation status (OP2) = Time-varying designation of whether or not a patient had undergone CSQM at any given point in time.

8) Waiting time (WAITTIME) = Time in years from unilateral cancer surgery to CSQM.

The cohorts are compared as those with unilateral invasive breast cancer some of whom were exposed to contralateral subcutaneous mastectomy at a variable time after initial surgery and some of whom were not exposed to contralateral subcutaneous mastectomy. The major endpoints are the finding of cancer recurrence, death or date of last follow-up. Death is corroborated by death certificate examination. Major prognostic factors for breast cancer survival and waiting-time bias are accounted for in the analyses.

Because the contralateral subcutaneous mastectomies were not done on a randomized basis, these data constitute an observational study. Survival is compared as crude survival and simple stratification by potential confounding variables and by Co proportional hazards modelling of disease-free survival which allows for simultaneous investigation of several covariates (both fixed and time varying). Time to death will be modeled (this was not done in the preliminary data analyses due to the small number of deaths in the contralateral subcutaneous mastectomy to the available point of follow-up, this is likely to change with extended time associated with the longer follow-up (minimum 10 years)).

The primary quantifiable selection factors for performing a contralateral subcutaneous mastectomy continue to appear to have been low nodal status and young age. These are readily modeled. Other selection factors for contralateral subcutaneous mastectomy e.g. socioeconomic status, positive family history of breast cancer, the patient's expressed wish for contralateral subcutaneous mastectomy, the presence of multicentric disease is being explored.

Data analyses with a larger and more robust control group is a critical component of the examination, including treatments other than mastectomy. Survival analysis models controlling for a greater number of potential confounders will be constructed and compared in the additional control cohorts.

Progress:

This IDEA proposal is designed within very severe budget constraints to follow-up on the preliminary observations of the data set forth in the proposal submitted in 9/95, from which funds were first available in late 8/96. Data analyses is not planned until completion of the follow-up of the cohorts and analyses of specimens.

The solution to the geographic (logistic) concerns raised by the reviewers was achieved by the hiring of Ms. Donna Silva who is based in Durham NC as the interviewer and Ms. Beata Pietrska as laboratory technician in Pittsburgh. Ms. Silva had worked with both Dr. Georgiade

and Dr. McCarty from 1985 to 1992, and was a welcome addition to the project when she rejoined them in 1996. Ms. Pietrska is new to the project in January 1997.

The project plan was and remains defined as six tasks. 1-Extend follow-up of contralateral cohort; 2-Acquire and compare additional control populations; 3-Model data sets; 4,5-Collate and catalogue pathology; 6-Resource availability

Task 1 - Extension of follow-up of patient cohort

Proposed (months 1-3):	Verification of Addresses; contact points; completeness of data in initial set.
Status	The inital contralateral cohort has been verified with copies of primary documents and incomplete data requirements defined, addresses and phone number at last known contact have been compiled. Data is complete for 88% of patients and is being pursued for the remaining patients.
Proposed (months 1-2):	Review of follow-up protocols
Status	The protocol has been finalized to acquire survival status and most recent clinical evaluation of tumor status, current medications and whether any additional cancer treatments had been used. Menopausal status and date (the vast majority of the original cohort have now entered menopause). Family history is revisited to determine new family members who may have had cancer diagnosed in the interval since the previous follow-up.
Proposed (months 4-16):	Patient follow-up contact; verify death certificates; chart reviews; missing person searches.
Status	Currently in progress. Anticipate completion of contacts, reviews, and verification of death certificates by January 98.
Proposed (months 17-24):	Verification of data sets; data analyses.
Status	Anticipated early 1998

Task 2 - Acquire and compare additional control populations

Proposed (months 1-4):	Explore sources comparison, NSABP sets.
Status	Identification of mastectomy, tylectomy and tylectomy with radiation groups from period comparable to target cohort available in biostatistical center. More detailed exploration of optimal strategy with biostatistician underway.

Proposed (months 5-16):	Match to initial patient characteristics
Status	Behind proposed schedule awaiting cohort data set completion
Proposed (months 17-24):	Data analyses, evaluation.
Status	Anticipated early 1998

Task 3 - Model

Proposed (months 1-24):	Model data analyses sets; establish parameter comparisons
Status	On schedule with re-examination of existing data ongoing to determine alternate considerations for analyses, considering bias, comparison with differing demographics of alternate therapy cohorts.

Task 4 & 5- Collate and catalogue the pathologic specimens
Evaluate the histology

Proposed (months 1-4):	Inventory histology sets; verify protocols; evaluate review instrument/protocol
Status	Review protocol complete (15,16), inventory of histology sets behind schedule due to lab move, personnel change. Project 10/97.
Proposed (months 2-12):	Prepare required recuts
Status	Delayed due to personnel change. Anticipate completion 11/97
Proposed (months 5-16):	Review histology; data entry
Status	Delayed due to personnel change and inventory delay. The budget not spent for first year will be used to increase time comitment of staff to complete this task in the next four months.
Proposed (months 17-19):	Resolve histology conflicts
Status	Anticipate on completion of set (4/98)
Proposed (months 17-24):	Data analyses
Status	On schedule

Task 6: Provides a means to make resource available to qualified and interested investigators

Proposed (months 1-24):	Inventory and characterize stability of stored samples, foster collaborations.
Status	On schedule

Further probing of 5-Year Survival Data demonstrates that there is a 12% difference in disease free survival advantage for the patients diagnosed before age 50 for the CSQM group, while UNI patients demonstrate no such difference. The difference in disease-free survival was greatest and most beneficial for CSQM patients compared to UNI patients plots when: Age < 50; Node positive- 1-3 Nodes positive; Tumor size > 2cm; Node positive and tumor size > 2cm. The reasons for this are being explored. It appears to be predominantly in the node negative group. A number of late recurrences have now been observed in the CSQM group initially contacted. Analyses of these data await the completion of the data set follow-up extension.

It has been estimated that differences in SES can account for a difference of as much as 25% in survival after breast cancer. CSQM were treated at private hospitals and the majority had some form of medical insurance. Appropriate matching for SES is being considered in the control groups. The CSQM group consist of only 4% black, while recurrence rates were similar for blacks and whites in the initial analyses and racial differences were unlikely to have accounted for survival differences between patient groups, this racial distribution will be considered further as data sets allow.

Conclusions:

The verification of the initial data set continues to support the rationale for the study. The project is following the proposed schedule in most areas and has accelerated in areas behind schedule to meet the SOW with the replacement of support personnel in late 1996, early 1997. The study of this unique population of patients is likely to advance our knowledge of breast disease and breast cancer in the sphere of diagnosis through the evaluation of the contralateral mastectomy for the frequency and distribution of epithelial hyperplasias associated with a contralateral cancer and, with completion of the dataset in this proposal, through the availability of this cohort to study molecular diagnostic probes on these lesions. It is also relevant that the observation of an apparent survival advantage in this cohort, confirmed with appropriate additional control groups in the present proposal, suggests the need to explore mechanisms for the apparent result, including silicone metabolites , steroid absorptions, and growth factor alteration/absorptions. In parallel with the present study, examination of silicone derivatives are being studied for effects on epithelial cells.

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Personnel Receiving Salary Support from first year budget	
Dr. Kenneth S. McCarty, Jr.	10% effort (full year)
Beata Pietrzak	100% effort (1/2 year)
Participants not receiving Salary Support from first year budget	
Dr. Nicholas Georgiade	5% effort
Dr. Gregory Georgiade	5% effort
Donna B. Silva	20% effort - Contribution in kind from funds - Dr. McCarty